

# FACT

## FOOD ANIMAL CONCERNS TRUST

411 W. FULLERTON PARKWAY, #1402W

POST OFFICE BOX 14599

CHICAGO, ILLINOIS 60614

1219 TO 101-6 10-10

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

April 6, 1999

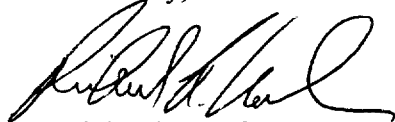
RE: Docket No. 98D-1146

To whom it may concern:

Enclosed please find the Comments of Food Animal Concerns Trust in response to the Food and Drug Administration's document entitled, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."

If you have any questions or need any additional information, please do not hesitate to contact us.

Sincerely,



Richard Wood  
Executive Director



Meryl Camin Sosa  
Manager, Food Safety Programs

98D-1146

PHONE (773) 525-4952 FAX (773) 525-5226

This stationery printed on recycled paper

D  
C19



**FOOD ANIMAL CONCERNS TRUST**

**411 W. FULLERTON PARKWAY, #1402W**

**POST OFFICE BOX 14599**

**CHICAGO, ILLINOIS 60614**

---

The Comments of Food Animal Concerns Trust  
in response to  
A Proposed Framework for Evaluating and Assuring the Human Safety of  
the Microbial Effects of Antimicrobial New Animal Drugs Intended for  
Use in Food-Producing Animals.

April 6, 1999

**Docket No. 98D-1146**

Food Animal Concerns Trust (FACT) is a non-profit organization that advocates for animal husbandry practices that will improve the safety of meat, milk and eggs. FACT's Food Safety Program makes recommendations to the federal regulatory agencies based on its review of the scientific literature. FACT's On-Farm Research Program develops husbandry methods that are humane, improve food safety, and reduce pollution. These comments address the Food and Drug Administration's (FDA) "Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals." FACT generally supports the Framework as an important step toward needed regulation.

**The on-farm use of antibiotics increases the pressure for antibiotic resistant bacteria to affect human health.**

It is now commonly recognized in scientific literature that the use of antibiotics in animal agriculture is a major cause of antibiotic resistant bacteria. This is due, in large part, to the sheer volume of antibiotics used on-farm non-therapeutically. It is estimated that more than 40 percent of all antibiotics manufactured in the United States are given to animals.<sup>1</sup> According to one study, 88 percent of all antibiotics used on-farm are used

---

<sup>1</sup> Levy, S., *The Challenge of Antibiotic Resistance*, Scientific American, March 1998.

**PHONE (773) 525-4952 FAX (773) 525-5226**

*This stationery printed on recycled paper*

subtherapeutically.<sup>2</sup> Among hogs, 93 percent receive antibiotics in their diets at some time during their “grower/finisher” period.<sup>3</sup> The actual quantity of antibiotics given to food animals is unknown due to the fact that feeds may contain antibiotics at concentrations higher than recommended levels.<sup>4</sup> Feed grade antibiotics do not require a veterinarian’s prescription.

The World Health Organization and major studies have recognized the threat to human health emanating from resistant bacteria that have food animal origins. For example, in 1969, the Swann Committee of the United Kingdom concluded that antibiotics used in human therapies, or those that promote cross-resistance, should not be used as growth promoters in animals.<sup>5</sup> In 1995, a task force of the American Society for Microbiology reported that “due to the increasing drug resistance in animal pathogens and changes in food production practices there is a growing threat to food, the food industry and hence the U.S. economy.”<sup>6</sup> The 1997, the World Health Organization report on “The Medical Impact of the Use of Antimicrobials in Food Animals” stated the following:

The magnitude of the medical and public health impact of antimicrobial use in food animal production is not known. Despite the uncertainty, however, there is enough evidence to cause concern. It is unrefuted that the use of antimicrobials leads to the selection of resistant bacteria....Timely public health action is needed to control or mitigate any

---

<sup>2</sup> National Research Council, Institute of Medicine, *The Use of Drugs in Food Animals: Benefits and Risks*, National Academy Press, Washington, DC, 1998, p. 130.

<sup>3</sup> Rothenberger, N., *Swine '95 – Antibiotic Usage in Premarket Swine*, National Animal Health Monitoring System Swine '95 Grower/Finisher Study, January 1996.

<sup>4</sup> In an examination of 3,328 feeds in the U.S. National Swine Survey, up to 25% of the feeds contained antibiotics at concentrations higher than the recommended levels. Dewey, CE, Cox, BD, Straw, BE, Budh, EJ, Hurd, HS. *Association between Off-label Feed Additives and Farm Sizes, Veterinary Consultant Use and Animal Age*. Preventive Veterinary Medicine. 1997, 31: 133-36.

<sup>5</sup> Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann Committee). London: Her Majesty’s Stationary Office; 1969.

<sup>6</sup> Report of the ASM Task Force on Antibiotic Resistance, American Society for Microbiology, Washington, DC, March 16, 1995, p. 1

medical problem that might be related to the widespread application of antimicrobials outside the medical sphere.<sup>7</sup>

Even the National Research Council Report acknowledged that antibiotic resistant bacteria can pass from food animals to humans, although they found the data to be inconclusive.<sup>8</sup> Finally, Wolfgang Witte observed that:

antibiotic use in animal husbandry is a driving force for the development of antibiotic resistance in certain pathogenic bacterial species. However, some claim that assessing the risk incurred by the use of antibiotics in animal husbandry must include documentation of cases in which treatment of a human infection failed because of antibiotic resistance of proven animal origin. Unfortunately, once a resistance gene has become widely disseminated, it is difficult to trace it back to its origin.<sup>9</sup>

In response to this widespread concern, following the Swann Report, European countries began taking steps to limit the use of the “older” antibiotics, such as penicillin and tetracyclines, as growth promoters.<sup>10</sup> More recently, the European Union decided to ban all antibiotics used subtherapeutically that have an impact on human therapies. To date, no preventative action has been taken by the U. S. government beyond responding to specific animal antibiotics on a case by case basis.<sup>11</sup>

---

<sup>7</sup> *The Medical Impact of the Use of Antimicrobials in Food Animals*, Report of a WHO Meeting, Berlin, Germany, October 13-17, 1997.

<sup>8</sup> National Research Council, Institute of Medicine, *The Use of Drugs in Food Animals: Benefits and Risks*, National Academy Press, Washington, DC, 1998, p. 125.

<sup>9</sup> Wolfgang Witte, *Medical Consequences of Antibiotic Use in Agriculture*, Science, vol. 279, February 13, 1998, p. 997

<sup>10</sup> It may be no accident that between 1994 and 1995, the USDA Cattle on Feed Survey found that the most common resistance among the animal Salmonella isolates was to tetracycline. Tollefson, Angulo, and Fedorka-Cray, *National Surveillance for Antibiotic Resistance in Zoonotic Enteric Pathogens*, Veterinary Clinics of North America: Food Animal Practice, March 1998, p. 145.

<sup>11</sup> For example, in approving the use of the antibiotic Baytril in cattle, the FDA obtained the agreement of the drug's sponsor, Bayer, to limit or stop the sale of Baytril if the FDA determines that its use in cattle leads to antibiotic resistance in bacteria that cause human disease. AnimalNet August 6, 1998.

**Producers, the animal drug industry, and government must take steps to reduce the resistance pressure coming from on-farm antibiotic use.**

Government action by itself will not succeed in relieving the resistance pressure that is a consequence of on-farm antibiotic use. Producers, veterinarians, the animal drug industry, and government must each respond as a part of a larger strategy.

Producers must employ on-farm practices that would minimize a reliance on antibiotics whether for subtherapeutic or therapeutic uses. The National Research Council Report identified where on-farm selection pressure is increased. By inference, this list becomes a set of critical control points where management strategies should be implemented in order to reduce the need for antibiotic intervention. These points are 1) the large concentration of animals with similar disease susceptibilities; 2) the social behavior of livestock which promotes transmission; 3) poor environmental hygiene, which promotes bacteria growth via water, feed, and bedding; 4) inadequate control over individual antibiotic dose and treatment; 5) the rapid turnover of animal populations without cleaning and disinfecting the facilities between groups; and, 6) the wide movement of carrier animals as breeding and feeding stock.<sup>12</sup> The National Research Council also noted the relationship of animal stress to the shedding of drug resistant bacteria.<sup>13</sup> The Swedish experience also endorses improved feed rations as a way to prevent disease and to promote growth.<sup>14</sup> Taken together, intervention at these critical control points may have the effect of reducing the need for antibiotics, either in subtherapeutic or therapeutic doses.

---

<sup>12</sup> National Research Council, Institute of Medicine, *The Use of Drugs in Food Animals: Benefits and Risks*, National Academy Press, Washington, DC, 1998, pp. 126-127.

<sup>13</sup> Id. p. 134.

<sup>14</sup> Following a total ban on antibiotic growth promoters, producers in Sweden found that improving feed quality compensated for the loss of the subtherapeutic drugs. *Antimicrobial feed additives*, Government Official Report no 132. Stockholm: Government of Sweden; 1997; and Centers Disease Control and Prevention presentation by Dr. Fred Angulo, Atlanta, GA, July 20, 1998.

Veterinarians and the animal drug industry need to implement the Prudent Use Guidelines, recently adopted by the American Veterinary Medical Association and other animal drug practitioners. While these guidelines address only the therapeutic use of antibiotics, a small percentage of total farm antibiotic use, it is still a significant step. Industry is also encouraged to develop alternatives to antibiotics for use with food animals. For example, results have been encouraging in the use of yeast,<sup>15</sup> bacteriocins,<sup>16</sup> and competitive exclusion<sup>17</sup> as antibiotic alternatives.

Government must take the necessary regulatory steps to ensure that public health is protected. Regulations currently address issues related to antibiotic residues and pathogen loads. The present regulatory structure does not address antibiotic resistance issues related to food animals. Given the current realities related to antibiotic resistance, this step must be taken.

**The Framework is an important step towards reducing the threat of resistant bacteria that is the result of on-farm antibiotic use.**

The Framework is an important step in government's response to the spread of antibiotic resistant bacteria. We support the FDA position that it is necessary to evaluate the resistance creating potential of a new antibiotic, both prior to and after its approval. Pre-approval resistance studies in themselves are not adequate since in many cases resistant bacteria emerge years following the introduction of the drug. A promising feature of the Framework is that it identifies actions to be taken based on the known

---

<sup>15</sup> Researchers in New Zealand have found that living yeast and bacteria can boost meat and egg production. AnimalNet October 9, 1998. See also Report by Dr. Stan Bailey of the Committee on Feed Safety, Report of the 100<sup>th</sup> Annual Meeting of the United States Animal Health Association, 1996 at page 169.

<sup>16</sup> Bacteriocins are naturally occurring antibiotic bacteria. Canadian researchers have found that bacteriocins act like ionophores to improve weight gain in cattle. AnimalNet, February 10, 1999.

<sup>17</sup> Bailey, JS, Cason, JA, and NA Cox, *Effect of Salmonella in Young Chicks on Competitive Exclusion Treatment* 1998 Poultry Science 77:394-399.

qualities of an antibiotic, and where there are unknowns, provides for surveillance. The Framework assesses the effect of proposed uses on the human pathogen load and bacterial resistance at the front-end, establishes resistance and monitoring thresholds, and requires post-approval monitoring at the back-end.

The Framework was precipitated by the Guidance for Industry Document 78, which stated that it is necessary to evaluate the human health impact associated with the uses of antimicrobial new animal drugs. FACT supports the Framework's human health imperative. At the same time, a second assessment should also be made regarding the approval's implication on animal health in terms of resistance. Will a particular approval render currently approved antibiotics ineffective for animal therapy due to the nature of the resistant bacteria that may result? Are there alternative treatments available to remedy the animal disease?

**Regulations are needed to fully address the issue of antibiotic resistance.**

The FDA states that in making the Framework available to the public, it is seeking to determine whether its concepts will be sufficient to ensure that "significant human antimicrobial therapies are not lost due to use of antimicrobials in food-producing animals."<sup>18</sup> In a footnote, the Framework states that "if finalized and implemented, [the Framework] will be part of the approval of new animal drug applications...."<sup>19</sup> However, it is not otherwise clearly stated if the intent of the FDA is to codify the Framework into regulations with the force of law. FACT calls on the FDA to translate the Framework into regulations following closure of the Framework's comment period. The Framework then would have the force of law and could be enforced as such. If requirements relating

---

<sup>18</sup> A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals January 6, 1999 (the "Framework") at p. 2.

<sup>19</sup> Id. At 7.

to antibiotic resistance are included in something other than a regulation or a statute, the enforceability of such requirements may be questionable and subject to judicial challenge.

The Framework is an opportunity for the FDA to fully address the issue of antibiotic resistance. Thus, the new regulations should provide the FDA with explicit authority to withdraw any approved antibiotic, old or new, when it is deemed to be a public health risk as defined by the Framework. The FDA, on numerous occasions, has articulated the position that it has limited authority to act with respect to antibiotics because it believes that it does not have the legal authority to do so.<sup>20</sup> For example, the FDA has stated that it cannot act to withdraw antibiotics from the market except through a lengthy, time-consuming judicial process where CVM must show, on a case-by-case basis, that the use of challenged animal drugs are unsafe or pose an immediate public health hazard.<sup>21</sup> Explicit articulation of FDA's authority with respect to animal antibiotics will eliminate uncertainty and will allow FDA to protect consumers from problems associated with antibiotic resistance. Further, the inclusion of requirements for public notice and public participation will make the processes related to animal pharmaceuticals more transparent and open to public scrutiny.

---

<sup>20</sup> Recently, Center for Veterinary Medicine ("CVM") Director Stephen Sundlof said FDA does not appear to have the legal authority to enact a blanket ban on seven animal drugs. *Sundlof says CVM lacks legal authority for blanket antibiotic ban*, Food Chemical News, March 22, 1999 at 4.

<sup>21</sup> Linda Tollefson, FDA-Center for Veterinary Medicine, said that any move to eliminate subtherapeutic drugs from the market must be conducted under constitutional due process, meaning the effort could take many years. *Veterinary Surveillance Program in Jeopardy without FSI Funding*, Food Chemical News, September 7, 1998, at 20-21. CVM Director Stephen Sundlof said that the only method currently available for withdrawing drugs from the market would be for CVM to determine whether the drugs are unsafe or pose an imminent public health hazard and this is a difficult legal threshold. Sundlof says CVM lacks legal authority for blanket antibiotic ban, Food Chemical News, March 22, 1999, at 4.



### **The Framework must apply to current approvals.**

The Framework is incomplete because it fails to address prior antibiotic approvals. The veterinary community is addressing the use of existing therapeutic antibiotics via its Prudent Use Guidelines. Other than the National Antimicrobial Resistance Monitoring System (NARMS) there is no FDA strategy in place to protect human or animal health due to resistance that may occur as a result of current antibiotic approvals. Meanwhile, not only is drug resistance becoming more common<sup>22</sup>, it is also being expressed in the form of multi-resistant bacteria.<sup>23</sup>

The new regulations should apply the Framework and its post approval monitoring provisions to antibiotics currently in use. Otherwise, prior approvals would meet one standard and post approvals another. This regulation would create a level playing field among producers of animal drugs approved by the FDA prior to implementation of the Framework and producers of animal pharmaceuticals approved after the new Framework regulations were created.

---

<sup>22</sup> For example, fluoroquinolone resistant bacteria have begun appearing since the first approval of fluoroquinolones for use with broilers. Following approval of a fluoroquinolone (enrofloxacin). for use in food animals in the United Kingdom, decreased susceptibility to ciprofloxacin rapidly emerged among human *Salmonella* isolates. Angulo, FJ, Tauxe, RV, and ML Cohen, *The origins and consequences of antimicrobial-resistant nontyphoidal Salmonella: implications for use of fluoroquinolones in food animals* (1998) at 4. Further, an increase in quinolone-resistant *Campylobacter jejuni* infections in Minnesota has been occurring since 1992. The percentage of *C. jejuni* isolates submitted to the Minnesota Department of Health that were resistant to nalidixic acid increased from 1.5% in 1992 to 9.0% in 1997. All nalidixic acid-resistant isolates from 1996-1997 were also resistant to the fluoroquinolone ciprofloxacin. Fluoroquinolones were approved for use in poultry in the United States in 1995. The authors of the Minnesota study believe that poultry is a likely source for domestically acquired ciprofloxacin-resistant *Campylobacter* infections in Minnesota residents. Smith, KE, Besser, JM, Leano, F., Bender, JB, Wicklund, JH, Johnson, B, Hedberg, CW, Vought, K, MacDonald, KL, and MT Osterholm, *Fluoroquinolone-Resistant Campylobacter*, American Association of Food Hygiene Veterinarians News-O-Gram Vol. 22, No. 2 at 3-4.

<sup>23</sup> Glynn, MK, Bopp, C, DeWitt, W., Dabney, P., Mokhtar, M, and FJ Angulo, *Emergence of Multidrug-Resistant Salmonella Enterica Serotype Typhimurium DT104 Infections in the United States*, 1998 New England Journal of Medicine 338:19 at 1333-1338. See also, Meng, J, Zhao, S, Doyle, M, Joseph, S, *Antibiotic Resistance of E.coli in Animals, Food, and Humans*, Journal of Food Protection, November 1998.

FACT supports the Framework's dual focus on both resistant and pathogenic bacteria in current and future approvals. While antimicrobials are needed to prevent the spread of foodborne pathogens, their use may disturb the intestinal flora so that bacteria may actually flourish. Pathogenic bacteria deserve the same level of attention, in the on-farm monitoring schemes, as do resistant bacteria.

**Category I antibiotics intended for subtherapeutic animal use must not be approved.**

Antibiotics that are “essential for treatment of a serious or life threatening disease in humans for which there is no satisfactory alternative therapy” should not be approved under any circumstances for subtherapeutic use with animals. FACT wants Category I to be revised so there will be no approvals of non-therapeutic antibiotics in this section. Given the danger of resistance to human health and the length of time involved in removing a drug from the market, a drug that falls into this category should only be approved for use as a therapeutic drug requiring a veterinarian’s prescription.

**On-Farm post-approval monitoring is necessary, so that timely mitigation steps can be taken.**

FACT supports on-farm post approval studies and monitoring as an early warning system to detect resistance following approval. FDA certified laboratories should test the samples with results made available to the public. The data collected could be joined with resistance data collected through NARMS and FoodNet (which monitors pathogens in the human population).

Numerous questions need to be addressed before an on-farm monitoring program is established. Who has the authority to collect the samples from the farm? What kind of verification procedures would be put into place? Would the data collection be drug

specific? What specific steps would be taken if resistance occurs? What kind of assistance would be in place to help producers respond to any resistance problems?

There has been some argument about collecting this data later in the food delivery system, perhaps at the slaughterhouse door. To do so would miss the opportunity to implement on-farm mitigation strategies if resistance were occurs. On-farm monitoring is an important part of the Framework.

**Manufacturers should be required to report sales data on all antibiotics intended for animal use.**

Finally, FACT applauds the inclusion of the reporting requirement in the Framework.<sup>24</sup> Obtaining detailed sales information for animal pharmaceuticals is crucial in researching and monitoring the link between animal drug use and rising resistance.

For example, how much sarafloxin is being used in treating chickens? Regarding subtherapeutic drugs, licensed feed mills report the pounds of feed sold, but how much active ingredient is in the feed? Health officials in Denmark were able to track an increase in the use of avilamycin as a growth promoter for broilers and pigs, as well as a measure their resistance to this antibiotic.<sup>25</sup> Similarly, researchers in Sweden were able to show that the Swedish ban on antimicrobial growth promoters effectively reduced the prevalence and degree of antimicrobial resistance.<sup>26</sup> In the U.S., we can measure the resistance but not the usage. An important link is missing. Clearly, reporting sales and volume data for animal pharmaceuticals sold in the United States is crucial to an understanding of the antibiotic resistance issue.

---

<sup>24</sup> The Framework at p. 18.

<sup>25</sup> Frank Møller Aarestrup, *Association Between Decreased Susceptibility to a New Antibiotic for Treatment of Human Diseases...and Resistance*, Microbial Drug Resistance, Vol. 4, No. 2, 1998, Mary Ann Liebert, Inc., p. 138.

<sup>26</sup> Van den Bogaard, A, London, C, Drieoson, D, and Stobberingh, E, *The effect of antimicrobial growth promoters on the resistance of fecal indicators*, University Hospital Maastricht, Department Medical Microbiology, The Netherlands.

Again, the reporting requirement should be included in a regulation so that it has the force and effect of law. Also, this requirement should be extended to apply to manufacturers of old antibiotics so that antibiotic resistance can be monitored in old antibiotics where it is equally, if not more, important to do so.<sup>27</sup>

While the animal pharmaceutical industry may contend that such information is difficult to obtain,<sup>28</sup> COMISA, the international animal health association, provides sales and volume data for the major fluoroquinolones in more than 30 countries.<sup>29</sup> Further, the human health pharmaceutical industry has been willing to release sales and volume data on antibiotics used in humans. Absent the release of sales and volume data by the United States animal health industry, FDA's ability to establish and monitor antibiotic resistance thresholds is questionable.

## Conclusion

The Framework constitutes an important step toward needed regulation, particularly in its recognition of the major impact of on-farm usage of antibiotics for non-therapeutic uses. Producers must employ on-farm husbandry practices that will minimize reliance on antibiotics, whether for therapeutic or non-therapeutic uses. Management strategies should be implemented in order to reduce the need for antibiotic intervention. In addition, research into antibiotic alternatives should be encouraged and the results utilized.

Regarding the Framework, FACT applauds the inclusion of pre-approval studies, post-approval monitoring surveillance systems and the creation of thresholds, as

---

<sup>27</sup> Since CVM Director Sundlof has stated that CVM lacks legal authority for a blanket ban on certain old antibiotics, and that any decision regarding withdrawal would need to be made on a case-by-case basis, by requiring monitoring of antibiotic resistance of old antibiotics, Director Sundlof will be able to make such determinations.

<sup>28</sup> *Sundlof says CVM lacks legal authority for blanket antibiotic ban*, Food Chemical News, March 22, 1999 at 4.

<sup>29</sup> Food Chemical News, June 22, 1998, at 24-25.

mechanisms for determining the occurrence of antibiotic resistance in new approvals. We also agree that establishing sales and volume data reporting requirements is an essential component of the new regulatory scheme. This sales data, along with on-farm resistance monitoring, will help establish an early warning system regarding the occurrence of resistant bacteria.

However, the Framework is inadequate in the following respects. First, the Framework's post approval surveillance must be extended to existing antibiotics, approved prior to the Framework's implementation. Second, Category I should be revised so that no non-therapeutic antibiotics will be considered in this section. Finally, the FDA also needs to assess what resistance impact an antibiotic's approval will have on animal health.